being enabling for antisense inhibition of damage-specific DNA binding protein 1, P127 expression *in vitro* does not reasonably provide enablement for *in vivo* antisense inhibition of expression of damage-specific DNA binding protein 1, P127; the Examiner cites several articles to support this position. Applicants respectfully traverse this rejection of the claims.

Applicants disagree with the Examiner's suggestion that cited references support the position that application of antisense *in vivo* is highly unpredictable.

The Examiner has pointed to articles concerning the technology of antisense oligonucleotides to support the view that antisense technology is unpredictable. However, when one reads each of the papers as a whole, as required under MPEP 2141.02, these references actually teach the potential usefulness of this class of drugs in humans, and more importantly fail to provide any reasonable basis to doubt the pharmacological activity observed in cells in the instant invention would also occur in cells in animals and humans.

The paper by Crooke is a review paper on the basic principles of antisense therapeutics. The pages pointed to by the Examiner that would supposedly concern extrapolations from *in vitro* uptake studies to predictions about *in vivo* behavior do not support the

statements made by the Examiner that cell culture examples are generally not predictive of *in vivo* inhibition of target genes. Statements by the author at these pages do not demonstrate the unpredictability of antisense oligos *in vivo*. Data in cells are used routinely, however, as predictors of pharmacological activity in animals and humans. It is a fundamental principle of drug development that data from whole cell studies, such as are provided in Example 15 of the instant specification, are directly applicable to predicting *in vivo* activity. The teachings of the paper by Crooke provide no reason to doubt that this fundamental principle is applicable to antisense agents.

In fact, statements in the paper by Crooke support the fact that development of antisense drug products is viewed by those of skill in the art as being the same as development of any other drug product in terms of applying the basic principles of pharmacology. For example, on page 22, first paragraph, Crooke points out "...numerous well-controlled [pharmacological] studies have been reported in which antisense activity was conclusively demonstrated [*in vitro*]." The key according to Crooke is the careful design of the *in vitro* studies to carefully evaluate dose-response relationships and antisense mechanism, similar to the type of

studies presented in the instant specification. Therefore, what this paper, and the other cited by the Examiner actually teach is that antisense oligonucleotides must be developed using well designed studies that progress logically from activity in cells to activity in animals and humans. Nowhere in the reference does the author state or suggest that results of well-designed *in vitro* pharmacological studies would not be predictive of activity *in vivo*.

Moreover, the paper by Branch (1998) teaches the need to develop antisense molecules based on sound data and careful screening, such as is presented in the instant specification. Nowhere does the paper state that extrapolation from *in vitro* data to *in vivo* effects is unpredictable.

The paper by Agrawal et al. cited by the Examiner was not provided with the Office Action. However, the paper of which the Applicants is aware is a review paper from 1996 on the technology of antisense. Like the papers discussed above, nowhere does this paper state that extrapolation from *in vitro* data on antisense compounds to *in vivo* effects is unpredictable.

The paper by Gewirtz et al. (1996) is another older paper on antisense technology. Like the other papers cited by the Examiner,

this paper only reviews issues that have arisen during development of the technology. Nowhere does this paper state that extrapolation from *in vitro* data on antisense compounds to *in vivo* effects is unpredictable.

However, Applicants have amended claim 15 and canceled claims 16-20 in an earnest effort to advance the prosecution of the case. Applicants reserve the right to file a continuing application directed to this subject matter without prejudice. Withdrawal of the rejection is requested in light of these amendments.

II. Rejection of Claims Under 35 U.S.C. 103(a)

Claims 1, 2 and 4-15 have been rejected under 35 U.S.C. 103(a) as being unpatentable over Dualan et al. (GenBank Accession No. U18299), in view of Taylor et al. (1999), Milner et al. 1997), Baracchini et al. (US Patent 5,801,154), and Hayes et al. (1998). The Examiner suggests that it would have been *prima facie* obvious to one of ordinary skill to design and use antisense for inhibition of damage-specific DNA binding protein 1, P127 expression since the sequence was taught by Dualan et al., and since Taylor et al. teaches antisense oligonucleotides can be designed to inhibit any gene of known sequence. The Examiner suggests that motivation is provided by Hayes et al. in teaching the role of this gene in repair of DNA damage, while Baracchini et al. teach the claimed

modifications. Further, the Examiner suggests that Milner et al. provide a reasonable expectation of success because they teach methods for screening for antisense activity. Applicants respectfully disagree with the Examiner suggestion regarding the teachings in the cited art.

Dualan et al. disclose only the sequence of a damage-specific DNA binding protein of a sequence referred to by GenBank Accession No. as U18299. This sequence is not the same sequence as the damage-specific DNA binding protein 1, P127 gene cited and claimed as a target for antisense in claims 1, 2 and 4-15. Therefore, this reference does not even teach the sequence of the gene targeted in the instant invention and listed as SEQ ID NO: 3 and referred to as GenBank Accession No. NM_001923.1. Further, nowhere does this reference teach or suggest antisense compounds of any type targeted to damage-specific DNA binding protein 1, P127 nucleic acid molecules as claimed. Therefore, this primary reference fails to teach the limitations of the claims.

The secondary references cited fail to overcome the deficiencies in teaching of this primary reference.

Taylor et al. (1999) discuss the use of antisense as a way to determine function of genes. Although this paper states that antisense can be designed to inhibit any gene whose sequence is

known, this paper does NOT state that such antisense are expected to inhibit gene expression. It is only with testing of the individual antisense compound, such as are provided for in the instant specification, that one can know if antisense compounds are capable of inhibiting gene expression. Moreover, nowhere does this reference teach or suggest antisense compounds of any type targeted to damage-specific DNA binding protein 1, P127 nucleic acid molecules as claimed. Therefore, this reference also fails to teach the limitations of the instant claims.

Milner et al. teach a method for identifying antisense oligonucleotides using optimization techniques where the antisense oligonucleotides have 1-17 bases and target sequences of a gene. However, nowhere does this paper teach or suggest antisense oligonucleotides 8 to 50 nucleobases in length targeted to damage-specific DNA binding protein 1, P127 nucleic acid molecules as claimed.

Baracchini et al. (US Patent 5,801,154) teaches methods of modifying antisense oligonucleotides to enhance activity. However, nowhere do this patent teach or suggest antisense oligonucleotides 8 to 50 nucleobases in length targeted to damage-specific DNA binding protein 1, P127 nucleic acid molecules as claimed.

Hayes et al. (1998) disclose that damage-specific DNA binding protein can function as a transcriptional partner to E2F1, making it a target for E2F regulation. However, nowhere does this paper teach or suggest antisense oligonucleotides 8 to 50 nucleobases in length targeted to damage-specific DNA binding protein 1, P127 nucleic acid molecules as claimed.

To establish a *prima facie* case of obviousness, three basic criteria must be met. MPEP 2143. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art must teach or suggest all claim limitations. Clearly, the combination of prior art cited fails to teach or suggest the limitations of the claims as amended, which claim antisense compounds targeted to the damage-specific DNA binding protein 1, P127 of SEQ ID NO: 3. A mere teaching of antisense in general does not render obvious the development of specific antisense compounds targeted to a specific sequence. The fact that the Examiner has cited a different damage-specific DNA protein sequence is not appropriate for making a case for obviousness. Further, the motivation to combine references must be provided by

the references themselves, not by the teaching of the instant specification (see MPEP 2143.01). Thus, this combination of art cannot render the instant claimed invention obvious. Withdrawal of this rejection is therefore respectfully requested.

III. Conclusion

Applicants believe that the foregoing comprises a full and complete response to the Office Action of record. Accordingly, favorable reconsideration and subsequent allowance of the pending claims is earnestly solicited.

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached page is captioned "**VERSION WITH MARKINGS TO SHOW CHANGES MADE**."

Respectfully submitted,

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Claims:

Claims 16-20 have been canceled without prejudice.

Claim 15 has been amended as follows:

15. (amended) A method of inhibiting the expression of Damage-specific DNA binding protein 1, P127 in cells or tissues comprising contacting said cells or tissues *in vitro* with the compound of claim 1 so that expression of Damage-specific DNA binding protein 1, P127 is inhibited.